

Remarks

Currently pending in the application are claims 1-14. Applicants respectfully request reconsideration by the Examiner, and advancement of the application to allowance.

35 U.S.C. § 103

Claims 1, 5 and 10-14 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Pastan et al. (U.S. Pat. No. 5,635,599) in view of Wen et al. (1993, Blood 82:1507-1516). Claims 1-4, and 6-9 under 35 U.S.C. § 103(a) are also rejected as being unpatentable over Pastan et al. in view of Wen et al. and further in view of Chaudhary et al. (1989, Nature 339:394-397) and Cousens et al. (U.S. Pat. No. 4,751,180).

The basis for the rejection is that Pastan et al. teach that a good choice for an "opening site" is a site tolerant to amino acid substitution and not highly conserved between closely related proteins in an alignment. While Pastan et al. do not teach a working example of circular permuted EPO nor a sequence of EPO, Wen et al. teach amino acid sequences for native EPO in human, Cynomolgous monkey, Rhesus monkey, mouse, rat, sheep, pig, cat, and dog that can be aligned to show the sites where the amino acid substitutions may specifically occur. However, Pastan et al. do not teach the selection of an opening site through a comparison of the non-conserved amino acids of a single protein as found native in multiple biological species.

Furthermore, the Examiner maintains that it would have been obvious to combine the teachings of Pastan et al. and Wen et al. with the teachings of Chaudhary et al. and Cousens et al., and arrive at a circular permuted EPO having a linker between the two portions of the circular permutein.

Pastan et al. teach a good candidate for an opening site can be found in a region of non-conserved amino acids where the protein is a member of a family of related proteins. Col. 8, ls. 45-67. Pastan et al teach a comparison of family members of proteins, that is, the comparison of different proteins. The teaching of Wen et al. is not a sequence comparison of a family of proteins, but rather, a comparison of native protein in different biological species.

Pastan et al do not teach that breakpoints are found at a single non-conserved amino acid position. Pastan et al teach the analysis of a segment of amino acids, a segment that is at least 5 contiguous position, usually about 10 to about 50, more usual about 15 to 40. Col. 8, ls 62-67. It is within that non-conserved region of amino acids (up to 50 amino acids in length) that a good breakpoint candidate may be found. Hence, properly read, Pastan et al suggests to look a the different sites within a region that is conserved among protein families.

Pastan et al also teach that the substitution of the amino acids and/or modifications of the side chain should not change the activity of the protein. However, neither Pastan et al nor Wen et al teach or suggest that the protein activity of EPO will remain unaltered if any amino acid is substituted. Furthermore, neither Pastan et al nor Wen teach protein activity will be unaltered or improved by substituting amino acids shown by an alignment of sequences of the same native protein in multiple species. Neither Pastan et al nor Wen et al teach a substitution of any amino acid that will not change the activity or protein folding of EPO.

On the other hand, Wen et al teach that "direct information on the three-dimensional structure of EPO is not yet available." Wen et al at 1507. Wen et al further teach a more complete set of animal sequences would be useful for "sequence based computer modeling of three dimensional structure" and a "larger data base would permit identification of highly

conserved domains likely to be crucial to folding and/or biologic function.” *Id.* Moreover, many of the amino acid sequences of EPO as found in various species are merely predicted. See e.g, Fig. 5.

As to the teachings of Chaudhary et al. (1989, Nature 339:394-397) and Cousens et al. (U.S. Pat. No. 4,751,180), both teachings are directed to fusion proteins and not circular permuted molecules. Linkers of Chaudhary and Cousens prevent two fused proteins from interfering with one another. By contrast, the linkers joining the circular permuted molecules of the present invention are used to properly position the amino acids on each side of the linker. The linkers of the present invention also allow the protein to properly fold and serve a much different function than the linkers of Chaudhary and Cousens. There is no motivation for one skilled in the art to combine the teachings of Chaudhary et al and Cousen et al with Pastan et al nor Wen et al to arrive at the subject invention.

35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-14 under 35 U.S.C. §112, first paragraph, for lack of enablement on the basis that the specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims.

Specifically, the Examiner asserts Pastan et al. teach highly conserved sequences are critical for biological activity. The Examiner then asserts that Wen et al. teach that residues 23, 24, 28, 29, 37-49, 51-53, 56, 78, 79, 85-87, 108-110, 112-115, 117 and 129-132 are conserved among nine mammalian EPO sequences in view of Wen et al. The Examiner concludes that one skilled in the art, absent data to the contrary, would reasonably expect that EPO circular

permuteins having an opening site at one of these conserved residues would not have biological activity. Based on Pastan et al. and Wen et al., in the instant case, 25 of the 49 species recited in claim 1 are deemed non-enabled.

The test for enablement of the claimed methods of use is undue experimentation, and not proof of biological activity, efficacy, safety, or other utility. The *Wands* court has identified a list of eight factors by which an examiner or reviewing court can assess whether a disclosure is sufficient to enable one of ordinary skill in the art to practice a claimed invention throughout its scope without having to engage in undue experimentation: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d at 737, 8 U.S. P.Q.2d at 1404 (citing *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986)). “A considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” *In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404 (quoting *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982)). The undue experimentation requirement, as part of the enablement requirement of § 112, involves a balancing of the results of a factual inquiry into the *Wands* factors as they apply to the circumstances of a particular case.

The specification enables each of the claimed polypeptides and provides support for making and using them. The amount of direction and guidance provided in the specification to make the claimed polypeptides is sufficient for one skilled in the art. The specification teaches

how to recombinantly make EPO molecules of the present invention. *See, U.S. Pat. App. Ser. No. 08/954,954* at 27, beginning line 4 to page 37, line 10; *Id.*, Example 1 at 42, beginning line 35 to page 44, line 7. The specification also teaches determination of the amino and carboxyl termini of the claimed EPO molecules. *Id.* at 25, beginning line 29 to 27, line 30. The specification further teaches determination of the linker. *Id.* at page 23, beginning line 35 to page 25, line 24. The specification additionally teaches assays for testing the claimed EPO molecules. *Id.* at 40, beginning line 8 to page 42, line 24. The specification teaches how to use the claimed EPO molecules. *Id.* at 15, beginning line 23 to page 16, line 2; *Id.* at 20, beginning line 21 to page 23, line 29. Any gap between the disclosure of the subject application and the breadth of the claims may be resolved without undue experimentation.

The breadth of the claims at issue is limited. It is a finite number of molecules that are claimed. Furthermore, even if the breadth of the claims were 100 species, no working example is required. *See e.g., In re Strahilevitz*, 668 F.2d 1229, 212 U.S.P.Q. 561 (C.C.P.A. 1982)(where the claims at issue were broad and applicants had described the invention with specificity, but had not disclosed even a single operative embodiment). The only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims, not the number of species embodied by the claims. Clearly, the specification teaches one skilled in the art how to make and use the claimed polypeptides, and there is no doubt as to the truth of these statements contained therein.

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Conclusion

In view of the remarks, Applicants respectfully submit that this application and all pending claims are now in a condition for allowance.

Respectfully submitted,

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